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The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic-Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification

Frank C. Detterbeck, MD, Edith M. Marom, MD, Douglas A. Arenberg, MD, Wilbur A. Franklin, MD, Andrew G. Nicholson, MD, William D. Travis, MD, Nicolas Girard, MD, Peter J. Mazzone, MD, Jessica S. Donington, MD, Lynn T. Tanoue, MD, Valerie W. Rusch, MD, Hisao Asamura, MD, Ramon Rami-Porta, MD FETCS, on behalf of the IASLC Staging and Prognostic Factors Committee, Advisory Boards and the Multiple Pulmonary Sites Workgroup

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Frank C. Detterbeck MD,[1] Edith M. Marom MD,[2] Douglas A. Arenberg MD,[3] Wilbur A. Franklin MD,[4] Andrew G. Nicholson MD,[5] William D. Travis MD,[6] Nicolas Girard MD,[7] Peter J. Mazzone MD,[8] Jessica S. Donington MD,[9] Lynn T. Tanoue MD,[10] Valerie W. Rusch MD,[11] Hisao Asamura MD[12] and Ramon Rami-Porta MD FETCS,[13] on behalf of the IASLC Staging and Prognostic Factors Committee, Advisory Boards and the Multiple Pulmonary Sites Workgroup[14]

[1] Department of Surgery, Yale University, New Haven, CT, United States of America
[2] Department of Diagnostic Imaging, Tel-Aviv University, Ramat Gan, Israel
[3] Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States of America
[4] Department of Pathology, University of Colorado, Denver, CO, United States of America
[5] Department of Histopathology, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, United Kingdom
[6] Department of Pathology, Sloan-Kettering Cancer Center, New York, NY, United States of America
[7] Respiratory Medicine Service, Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France
[8] Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, United States of America
[9] Department of Thoracic Surgery, New York University, New York, NY, United States of America
[10] Department of Internal Medicine, Yale University, New Haven, CT, United States of America
[11] Thoracic Surgery Service, Sloan-Kettering Cancer Center, New York, NY, United States of America
[12] Division of Thoracic Surgery, Keio University, School of Medicine, Tokyo, Japan
[13] Thoracic Surgery Service, Hospital Universitari Mutua Terrassa and CIBERES Lung Cancer Group, Terrassa, Barcelona, Spain
[14] See Appendix

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Abstract

Introduction: Application of tumor, node and metastasis (TNM) classification is difficult in patients with lung cancer presenting as multiple ground glass nodules or with diffuse pneumonic-type of involvement. Clarification of how to do this is needed for the forthcoming 8th edition of TNM classification.
Methods: A subcommittee of the IASLC Staging and Prognostic Factors Committee conducted a systematic literature review to build an evidence base regarding such tumors. An iterative process that included an extended workgroup was used to develop proposals for TNM classification.
Results: Patients with multiple tumors with a prominent ground glass component on imaging or lepidic component on microscopy are seen with increasing frequency. These tumors are associated with good survival after resection, and a decreased propensity for nodal and extrathoracic metastases. Diffuse pneumonic-type of involvement in the lung is associated with a worse prognosis, but also a decreased propensity for nodal and distant metastases.
Conclusion: For multifocal ground glass/lepidic tumors, we propose that the T category is determined by the highest T lesion with either the number of tumors or m in parentheses to denote the multifocal nature; a single N and M category is used for all the lesions collectively – e.g. T1a(3)N0M0 or T1b(m)N0M0. For diffuse pneumonic-type lung cancer we propose that the T category is designated by size if in one lobe, or as T4 if involving an ipsilateral different lobe or M1a if contralateral; a single N and M category is used for all pulmonary areas of involvement.

Introduction

In 1876 Malassez described a bilateral multinodular form of malignant lung tumor.[1] In 1903 Musser described a diffuse infiltrative type of lung cancer involving a single lobe or the entire lung simulating pneumonia.[2] In 1953 the presence of epithelial cells in the alveolar wall was confirmed by electron microscopy[3] and it was realized that neoplastic epithelium may extend along the alveolar surfaces without invasion or destruction of alveolar wall in a pattern referred to as "bronchioloalveolar carcinoma" (BAC).[4, 5] The non-invasive pattern of growth along the alveoli was described as "lepidic". For many years BAC was used to describe tumors which contain a lepidic component with or without an additional invasive component. During the last decades of the 20th century, accumulated data indicated small (<3cm) single tumors without an invasive component were nearly universally cured by resection.[6] Accordingly, the 1999 and 2004 editions of the WHO the classification lung tumors restricted the term "bronchioloalveolar carcinoma" to single purely lepidic tumors without any evidence of invasion.[7, 8] However, the new definition was not widely understood or accepted and in 2011 the term BAC was abandoned because it was being used ambiguously in many different contexts.[9]

Lepidic extension of tumor cells permits aeration of the alveoli and results in a characteristic appearance on computed tomography (CT) referred to as ground glass. In this review such lesions with prominent ground glass or lepidic features are referred to as (GG/L) nodules. Patients with multiple GG/L nodules are seen fairly commonly, perhaps due to an increasing prevalence of CT imaging; there is at least the perception that multifocal GG/L (or the identification thereof) is becoming more frequent, although the incidence has not been quantified.[10-12]

Similar to other situations with multiple pulmonary sites of lung cancer, there has been confusion about how to classify tumors with multifocal GG/L nodules.[13, 14] The International Association for the Study of Lung Cancer (IASLC) appointed a subcommittee of the Staging and Prognostic Factors Committee (SPFC) to address this and provide greater consistency in classification for the forthcoming 8th edition of the tumor, node and metastasis (TNM) classification of lung cancer. The full scope of this

effort is described in other papers.[15-17] This paper reports the work of this subcommittee for multifocal GG/L lung cancer and pneumonic-type of lung cancer.

The primary purpose of stage classification is to provide a nomenclature about the anatomic extent of disease in order to describe homogenous groups of tumors. A consistent nomenclature in turn has many applications, e.g. to describe aspects of the tumor in patients enrolled in clinical trials, as a factor in estimating prognosis after a particular treatment, etc. It is important to define what is meant by a homogeneous group: the most relevant criterion of homogeneity is to group tumors with a similar biologic behavior attributable to the tumor itself (as opposed to outcomes resulting from patient characteristics or treatment).

Paying attention to disease entities is particularly important for patients with multiple pulmonary foci of lung cancer because the biologic behavior varies dramatically – in terms of outcomes, the patterns of progression, and the issues they present regarding TNM classification. Therefore, the pattern of disease is a crucial aspect in defining homogeneous groups among patients with multiple lung tumors. We have structured our approach according to patterns of disease that are associated with a particular biologic behavior in order to find the most appropriate TNM nomenclature for each, taking into account the particular issues that each one presents. However, we recognize that it is not entirely clear whether each of these represents a truly distinct disease entity or just a variation within a larger group.

This paper summarizes the evidence base that was identified by this subcommittee specifically pertaining to lung adenocarcinoma presenting as multiple nodules with GG/L features. This effort focused primarily on data pertaining to patients with multiple sites of such disease, and does not constitute a comprehensive review of solitary sub-solid or lepidic lung cancer; for the latter we refer to other recent reviews.[9, 11, 18-20] This paper also addresses lung cancers with diffuse pulmonary involvement, often called pneumonic adenocarcinoma. This entity typically presents radiologically with varying areas of ground glass and consolidation, although the appearance is more regional and patchy than nodular. Microscopically, these tumors are typically invasive mucinous adenocarcinomas with a predominance of lepidic growth. However, while there are features of the appearance of pneumonic adenocarcinoma that have similarities to multifocal lung cancer with prominent GG/L features, many aspects of the behavior of these entities are different.

The evidence base was used to formulate criteria to identify these entities in order to provide guidance for consistent categorization. Taking into account the particular issues presented by these entities we provide guidance on how to apply the TNM classification to these tumors, in order to facilitate consistent classification and address the sources of confusion associated with lung cancer involving multiple pulmonary sites of malignancy.

Methods

The IASLC database[21] was not informative for this topic, because data on ground glass or lepidic features of lung cancers or on pneumonic-type adenocarcinoma was not captured. To develop an evidence base the multiple nodules subcommittee conducted a systematic review with a methodologist's help for relevant literature from 1995-2015, building on a prior systematic review of patients with multiple tumor lesions conducted by the American College of Chest Physicians (ACCP) for the Lung Cancer Guidelines (3rd edition).[22] Reference lists of identified articles were also examined, and each paper in the ACCP guideline was revisited to ensure correct data abstraction pertaining to the patients relevant to this review. The Population, Intervention, Comparator and Outcomes (PICO) questions, search structure, inclusion and exclusion criteria and results are available on request.

The identified evidence was reviewed and interpreted; an iterative process was used to develop a structure to identify homogeneous cohorts of tumors and propose how the TNM classification rules

should be applied to these cohorts. Successive drafts were discussed and circulated to the entire subcommittee for revision. The paper was then sent for critical review to an extended workgroup of individuals with particular interest and expertise in this topic (appendix) as well as further review and eventual endorsement by the entire SPFC.

Results: Multifocal Lung Cancer with GG/L Features

Evidence Base

Terms

A ground glass nodule (GGN) is defined as a focal nodular area of increased lung attenuation on a CT scan, through which normal parenchymal structures (i.e. airways and vessels) can be visualized (see Table 1 for glossary of terms). A GGN is purely ground glass; nodules with a solid component are referred to as part-solid lesions. The term sub-solid includes both pure ground glass and part-solid nodules.

The pathologic correlates of this radiographic appearance are adenocarcinoma subtypes, primarily lepidic predominant adenocarcinoma (LPA), minimally invasive adenocarcinoma (MIA), adenocarcinoma in situ (AIS) or atypical adenomatous hyperplasia (AAH), all of which have a predominant lepidic component (Table 1).[9] Lepidic refers to a growth pattern whereby atypical pneumocytes proliferate along alveolar walls (think of a butterfly [Order Lepidoptera] alighting on a branch but not disturbing it).

A term is needed to denote this pattern of disease, encompassing both the radiographic and histologic features of these cancers. The term GG/L addresses this, and includes both pure ground glass and part-solid nodules (radiographic appearance) and lepidic adenocarcinomas with or without an invasive component (histologic features).

Descriptive Characteristics

Numerous studies have consistently reported that multifocal GG/L lung adenocarcinomas occur mostly in women (60-80%), which is a contrast to NSCLC in general.[12, 23-29] This observation is made in both Asian and North American populations. The proportion of nonsmokers (30-80%) varies with the regional prevalence of smoking but is always greater than that of the general prevalence in patients with lung cancer in that region. These findings suggest a potential different etiology for multifocal GG/L lung cancers.

There is a general correlation between the radiographic (CT) appearance and histologic findings, but it is imperfect. Among multifocal tumors with a pure ground glass appearance, some (14-80%) were found to be invasive adenocarcinoma.[28-30] Of those that were >50% ground glass, some (0-85%) were reported to be pure BAC (2004 WHO definition) and some (15-100%) were reported as adenocarcinoma with BAC features.[29-31] The tumors in these reports would probably variously be classified as adenocarcinoma-in situ, MIA or LPA using the current WHO classification.[32] Advances in image quality and histologic definitions do not appear to adequately account for the variability. Studies involving primarily solitary sub-solid nodules note that lesions are reported as adenocarcinoma (with BAC features) in ~10% (7-30%) of pure GGN and ~50% (15-80%) of part-solid (>50% ground glass) lesions.[11, 23, 31, 33-42] Thus, while there is a general trend, radiographic findings do not correlate well with the histologic diagnosis. To an extent this suboptimal correlation may reflect ambiguities in the histologic terms (i.e. BAC), or interobserver variability in the radiographic characterization of nodules.[43]

Histologic and Molecular Characteristics

Although GG/L tumors are all adenocarcinomas, there are often differences between lesions with respect to proportions of adenocarcinoma subtypes. We surmise that many of these lesions could be considered separate primary tumors by a comprehensive histologic assessment.[44]. However, this has never been studied, and there may be a sizable proportion of lesions that appear similar.

Although intra-observer variability is low (κ = 0.78-0.87)[45] some inter-observer variability exists among dedicated thoracic pathologists in identifying the predominant subtype among lung adenocarcinomas in general (not specifically GG/L lesions).[45-47] In a study involving 100 consecutive adenocarcinoma cases and 5 dedicated thoracic pathologists, agreement on the predominant pattern was achieved in 66% (κ = 0.44-0.62).[45] In a study involving the evaluation of 19 typical cases for each of 5 adenocarcinoma subtypes by 26 thoracic pathologists, the predominant pattern was consistently identified in 92-100% of cases (except micropapillary with consensus in 62%).[47] On the other hand, in a study of 40 difficult cases and 51 thoracic pathologists, consensus on the predominant subtype of adenocarcinoma was achieved initially in 51-74% (lepidic 57%, papillary 63%, acinar 51%, micropapillary 64% and solid 73%).[46] Training improved these results somewhat (consensus in 60-75%).[46] There is also interobserver variability in identifying the presence of invasion.[47] In a study involving 28 thoracic pathologists who evaluated 64 typical and difficult cases for the presence of invasion, complete agreement was seen in 10% of cases, and <10% discordance in 29% (3 point scale: probable and definite invasion, unclear, probably or definitely not invaded; κ = 0.55 for typical cases and 0.15 for difficult cases).[47] How this inter-observer variability between cases might affect consistency of classifying invasion or the predominant subtype among different lesions in a patient with multiple GG/L tumors is unclear, and has not been studied.

Multifocal adenocarcinomas with lepidic features may be non-mucinous, mucinous or mixed. Among studies reporting on GG/L tumors ~50% (38-64%) are non-mucinous, ~35% (22-52%) mucinous, and ~15% (3-18%) mixed.[27, 48-50]

Clonality studies comparing these multiple lesions in a single patient are limited and conflicting. Recent studies suggest that most of these are separate primary cancers; in those patients with multifocal GG/L lung cancer in which clonality could be assessed 71-83% were discordant,[51-53] However, earlier smaller studies suggested either the same[54, 55] or separate lineage[56] for all lesions.

Biologic Behavior

An understanding of the innate biologic behavior of a cancer is provided by natural history studies (outcomes in the absence of any treatment intervention); an approximation of this can be gained from studies in which multifocal sub-solid lung cancers were observed for a period of time. In 3 studies specifically addressing multifocal GG/L lung cancer 60-95% of pure GGN remained stable, a few decreased or disappeared, and a few increased or became part-solid (prompting resection).[57-59] These studies involved 28, 23 and 23 patients (40, 89 and 196 nodules), with median observation periods of 24, 40 and 49 months, respectively.[57-59] This is consistent with a recent review,[11] involving mostly studies of solitary sub-solid nodules, in which the majority remained stable, ~20% decreased or disappeared, and 20% increased or became more solid (involving median observation periods of 9-50 months). The proportion that grew or became more solid was somewhat higher among part-solid nodules than pure GGN.

Outcomes after resection of multifocal GG/L lung adenocarcinoma has been reported to be excellent (~90% 5-year OS, Table 2). The studies listed have involved predominantly patients with multiple nodules which were largely part-solid. Despite this, the incidence of N2 node involvement has been low. This is consistent with other data that GG/L lung adenocarcinomas in general exhibit more indolent behavior.[11, 27, 60, 61] The risk of invasive cancer does not differ whether there is a single or multiple sub-solid nodule(s).[23, 28, 35, 57, 58, 62] On the other hand, data from the SEER registry from 1998-2002 involving patients coded as having multiple "BAC" lesions shows mediocre outcomes (Table 2): 48% 5-year OS for same-lobe multiple lesions (mostly resected) vs 7-25% 5-year OS when involving different lobes (but only 21% were resected).[27] We have little additional information about these patients (e.g. CT characteristics), and we must recognize the ambiguity of a diagnosis of BAC from this time period.

The pattern of recurrence of multifocal GG/L lung adenocarcinoma is shown in Table 3. Distant recurrence is distinctly unusual. Local recurrence and the appearance of new primary lung lesions are predominant; how a new pulmonary lesion is classified may account for some variability among these. Other studies involving mostly solitary GG/L lung cancers have also observed a decreased propensity for nodal or systemic spread and a marked increased propensity to develop additional pulmonary foci compared with NSCLC in general.[20, 24, 48, 61, 63-71]

Criteria Identifying Multifocal GG/L Tumors

It is important to define criteria by which we can recognize particular patterns of disease. The multiple nodules subcommittee developed the criteria shown in Table 4 for GG/L lesions. The rationale for these criteria are as follows. Recognizing this pattern of disease (multiple GG/L lesions) addresses a commonly encountered group of patients. There is a substantial body of evidence that this pattern of disease is associated with good outcomes and infrequent nodal or extrathoracic recurrences – i.e. a biologic behavior different than that of the more typical NSCLC presenting as a solitary, solid spiculated mass. Criteria for this pattern of disease must take into account the clinical presentation, because typically there are multiple foci, many of which are followed by serial imaging and not resected. Requiring a histologic characterization of each for pathologic classification would leave a large group (likely the majority) of such patients without a definition of how to classify them pathologically.

The pattern of GG/L nodules is essentially only seen with lung adenocarcinoma, so inherently there is some similarity between the lesions. Provided there are multiple tumors that have a prominent GG or lepidic component, categorization as multifocal GG/L tumors is appropriate; focusing on further differentiation among multiple GG/L tumors whether they have matching or only similar features on histologic examination is problematic for several reasons. We have no evidence that this is associated with a different behavior or outcomes. We have limited data in this setting about how well or consistently this can be done. Because there are often many lesions, there may often be a mixture of quite similar and less similar lesions, making categorization based on this histologic criterion complicated. Finally, a detailed histologic assessment approach is only applicable to resected lesions, and is problematic in its application to actual patients (who frequently have lesions that are simply followed). Therefore we propose that tumors be included under the rubric of multiple GG/L tumors whenever there are multiple nodules with ground glass or lepidic features (which inherently defines some similarity), regardless of finer nuances of histologic similarity among them.

GG/L tumors have a prominent proportion of GG or lepidic growth. Foci of AAH, however, are not counted; the multifocal GG/L category applies to multiple tumors that are AIS, MIA, LPA with or without other subtypes of adenocarcinoma, provided there is a prominent lepidic component. Furthermore, there should be multiple tumors with a prominent proportion of GG or lepidic growth.

While there is spectrum of ground glass vs solid or lepidic vs invasive components, the categorization of GG/L tumor should not be used for tumors that are completely or almost completely (i.e. ≥90%) solid or invasive. Stated differently, a solid (spiculated) lung cancer should not be categorized as a GG/L tumor simply because a small amount of lepidic growth is seen at the periphery. Furthermore, minute separate foci of neoplastic growth are not counted, recognizing that on careful review, a background of such lesions can often be found in the resected lung. A solid/invasive lung cancer should not be classified as a multifocal GG/L tumor because such small lesions are detected.

A patient with a solid or almost completely solid tumor and (an)other prominently GG or lepidic tumor(s) should be categorized as having separate primary tumors; indeed the histologic appearance would be different.

Proposal for the Application of TNM Classification to Multifocal GG/L Tumors

Multifocal GG/L lung adenocarcinoma should be classified by the T category of the lesion with the highest T, with the number (#) of lesions or simply (m) for multiple indicated in parentheses, and an N and M category that applies to all the multiple tumor foci collectively – e.g. T1a(4) N0 M0. According to new proposals described elsewhere,[72] the size is determined by the largest diameter of the solid component (by CT) or the invasive component under the microscope. The designation of Tis should be used for AIS and T1a(mi) for MIA (e.g. T1a(mi)(m) N0 M0).

All of the parenchymal tumors in both lungs are collectively captured by the T component – i.e. T(#/m) regardless of location (e.g. same lobe, different lobe or lung). The T component should include all tumors whether resected or not that are thought to be malignant (either suspected or proved). Furthermore, the T(#/m) multifocal classification should be applied to both grossly recognizable tumors as well as those that are only discovered on pathological examination (microscopically or otherwise).

Rationale

The T(#/m) designation has been a longstanding part of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) general rules for TNM classification, specifically for "multiple synchronous primary tumors of one organ".[73, 74] The multiple GG/L pattern of disease appears to be what this T(#/m) designation was intended for. The single T category for all pulmonary lesions together (including noting the T category of the lesion with the highest T) seems to be both practical and appropriate. It appears to be reflective of the prognostic impact of the tumor extent (i.e. the highest T lesion). Typically there are multiple lesions; sometimes counting an exact number can be difficult for the pathologist or radiologist and influenced by technical aspects of imaging. The T(m) designation remains easy to apply in such situations. The decreased propensity for nodal and distant metastases and increased propensity for additional lung lesions supports the concept of a single N and M for all of the pulmonary lesions.

Practical Concerns

We suggest that pure GGNs <5mm not be taken into account. Thinner slices (e.g. 1.25mm) and other technologic advances are desirable, as they provide greater sensitivity to detect faint GGNs or small solid areas.[75] We also suggest that tumors that are almost completely solid or invasive (i.e. have a ground glass or lepidic component of <10%) not be classified under this rubric; such tumors should be classified separately from tumors that have a significant ground glass/lepidic component. We recognize that these practical suggestions are arbitrary and not evidence based. Hence they should be viewed as suggestions and not as rules. Judgment is needed, especially for tumors that are near the boundaries that are inherent to any classification system.

Progression/Recurrence

New GG/L tumor(s) that develop in a patient with a previous (resected) multifocal GG/L adenocarcinoma should be classified as a new second primary cancer if no lesion was previously present at the site of the new GG/L tumor. Lesions that were previously simply observed but subsequently progress enough to warrant intervention should be designated by the current size and other characteristics of the lesion at the present time; stage classification is always linked to the time of assessment. For example, at the time of resection of a GG/L tumor(s), additional lesions may be noted but managed conservatively by observation (e.g. a pure GGN). If such lesion(s) subsequently progress (perhaps warranting resection), they should be designated by their characteristics at the current time (e.g. T1a(#/m) N0 M0); the fact that they were noted previously has no impact on the current TNM classification. A designation of recurrent disease is only applicable if there is clear evidence of recurrence of exactly the same tumor after a disease free interval.[73, 74]

Results: Pneumonic-Type of Lung Cancer

Evidence Base

Some patients exhibit a diffuse pattern of lung cancer similar radiologically to a pneumonia (hence the name "pneumonic-type of lung cancer").[48, 49, 65, 76, 77] This form of adenocarcinoma has some similarities to multifocal GG/L adenocarcinoma but also many differences. It is unclear whether this represents an extreme form of multifocal adenocarcinoma or a later stage in the evolution of this entity or a different entity altogether.

Garfield et al[78] reviewed the literature in 2008 and argued that mucinous and nonmucinous BAC are separate entities. This was based on a different putative cell of origin and differences between mucinous and nonmucinous BAC by immunohistochemistry (CK-20 in 53% vs 3%; TTF-1 in 24 vs 88%) and biomarkers (EGFR mutations in 3% vs 45%; Kras in 34% vs 14%, respectively).[78]

It is thought that the majority of pneumonic-type of adenocarcinomas are invasive mucinous adenocarcinomas, particularly with the 2015 WHO classification.[32] In the existing literature there is moderate correlation between imaging and histologic subtype (Table 5). Among mucinous tumors a consolidative pattern was noted in 33-75%,[49, 69, 79, 80] and 75% have areas of ground glass,[79] In addition, several studies reported no significant differences between mucinous and non-mucinous tumors in the proportion with a nodular vs a pneumonic presentation.[49, 69, 80, 81] Conversely, among the larger historical studies reporting specifically on pneumonic-type of lung cancer, ~45% (26-57%) are mucinous, ~40% (29-53%) non-mucinous and ~15% (12-21%) mixed (mucinous and non-mucinous) adenocarcinoma.[49, 69, 76]

Descriptive Characteristics

Demographic data is limited; the mean age of patients with pneumonic-type of lung adenocarcinoma has varied from 41-66 years, and the gender distribution is reported as either a preponderance of women or men, perhaps reflecting differences in definitions of terms or by geographic region.[76, 82] Others have reported no difference in age, gender or smoking status for pneumonic-type of adenocarcinoma compared with other forms of BAC.[33]

In the largest series (n=52) of pneumonic-type of adenocarcinoma consolidation was seen in 83%; in 63% there were additional areas of involvement in another lobe and bilateral disease in 58%.[76] This study involved surgical and non-surgical patients. In other series involving surgical patients the proportion of bilateral disease is lower.[69]

Histologic and Molecular Characteristics

Under the microscope it appears that pneumonic-type of adenocarcinoma typically has a homogenous appearance throughout, especially when the mucinous form is involved. However, this has not been formally studied or quantified, and it is less clear whether the non-mucinous or mixed forms are homogeneous or heterogeneous.

Limited investigation of clonality in pneumonic-type of adenocarcinoma has been carried out. A study of a patient with pneumonic-type of adenocarcinoma found evidence of different clonality in each of five lobes.[83] This involved immunohistochemistry (CA19-9, CEA, p53), PCR and fluorescence-based single strand conformation polymorphism and sequencing after cloning to compare p53 point mutations and specific DNA base pair substitutions.

Biologic Behavior

Patients with pneumonic-type of adenocarcinoma typically present without nodal or systemic metastases despite diffuse pulmonary involvement (Table 5); the occasional use of double lung transplantation as a treatment underscores this.[61, 84, 85] The observation that recurrence (which occurred in over half) was almost always confined to the (transplanted) lung[84-87] is both further evidence of the

unusual pulmotrophic nature of this entity as well as of our limited understanding of the process of metastasis and the microenvironment.

Data on outcomes after curative treatment is limited, presumably due to the diffuse nature; survival after resection is clearly worse than in patients with multiple distinct foci of GG/L cancers. Recurrences occur primarily in the remaining lung (Table 5).

Diffuse Miliary Adenocarcinoma

There are also patients who are found to have diffuse "miliary" foci of adenocarcinoma, sometimes noted only on histologic examination of lungs that appeared radiologically normal. Such patients have not been specifically studied enough to allow characterization of demographics, risk factors, or biologic behavior, but it is implied that they are similar to other patients with multifocal or pneumonic-type of lung cancer.[20, 70]

Criteria Identifying Pneumonic-Type of Lung Cancer

The multiple nodules subcommittee developed the criteria shown in Table 6 for pneumonic-type of adenocarcinoma with the following rationale. The diffuse consolidative, regional involvement is distinct from that of multiple GG/L nodules or the solitary mass of the typical primary NSCLC. The biologic behavior of this pattern of disease is also distinct, with a worse prognosis than multiple GG/L nodules, yet infrequent nodal or extrathoracic involvement.

Proposals for the Application of TNM Classification to Pneumonic-Type of Adenocarcinoma

In the case of a pneumonic-type of adenocarcinoma with a single area of tumor, it is straightforward to apply the TNM classification as described for lung cancer in general (e.g. the T category determined by size, N and M determined by nodal or extrathoracic involvement).[88, 89] In the case of multiple pulmonary sites of involvement, the T or M category should be determined by the location of the areas of involvement: T3 if confined to one lobe, T4 if involving different lobes in one lung, and M1a if involving both lungs. If the tumor involves both lungs, the T category should be designated according to the appropriate T category for the side with the greatest amount of tumor (i.e size or T3 if in one lobe, T4 if in more than 1 lobe on that side). The appropriate N category is chosen that applies to all pulmonary sites of the primary tumor collectively; pleural/pericardial tumor nodules or distant metastases will lead to an M1a or M1b designation. The classification should be applied to both grossly recognizable lesions as well as those that are only discovered on pathological examination (microscopically or otherwise). This classification scheme should be used for pneumonic-type of adenocarcinoma regardless of whether it is mucinous, non-mucinous or mixed. Furthermore, although it is generally the case that different areas of pneumonic-type of adenocarcinoma are histologically similar, the classification scheme should be applied without requiring a detailed histologic assessment to determine whether multiple details are exactly matching or not.

Particularly with the diffuse nature of pneumonic-type of adenocarcinoma, it can be difficult sometimes to define discrete boundaries. Because size may be difficult to determine, when the area of involvement extends into an adjacent lobe (as well as a discrete separate area of involvement in an adjacent lobe) the T4 designation should be applied (recognizing extension into another lobe). If the involvement is confined to a single lobe but hard to measure, a designation of T3 should be used.

We propose that the schema for application of TNM classification described for pneumonic-type adenocarcinoma also be used for miliary forms of adenocarcinoma. Because size of miliary involvement is inherently difficult to determine, miliary involvement in a single lobe should be classified as T3 without regard to size.

Rationale

The pneumonic-type of adenocarcinoma generally has a similar histologic appearance throughout. Therefore, there is a parallel to applying TNM classification as it is done for separate tumor nodules. A designation by the location of lobes that are involved seems practical for a diffuse disease in which measurement of size may be difficult. Furthermore, it stands to reason that the lobar extent of involvement may have prognostic value, although this has not been specifically reported. The decreased propensity for nodal and extrathoracic metastases supports the concept of a single N and M for the entire pulmonary areas of involvement.

A T category for multiple areas of pulmonary involvement also seems appropriate for miliary forms of adenocarcinoma. Although little data is available, the difficulty of linking an N or M site of involvement to a particular primary tumor site as well as the diffuse nature of the primary tumor involvement makes this appealing.

Discussion

We have structured our approach according to patterns of disease. Whether each of these represents a truly distinct disease entity or just a variation within a larger group can be debated. However, this is also a matter of semantics – e.g. is lung cancer one entity and squamous carcinoma and adenocarcinoma (or acinar predominant, LPA etc.) simply variations, or should we view these each as separate entities?

A review of available information on lung cancers presenting as multiple nodules with GG/L features reveals several distinctive characteristics. These tumors occur more frequently in women and nonsmokers, suggesting the influence of different etiologic factors compared to NSCLC in general. The rate of progression seems to be more indolent. There appears to be a decreased propensity for nodal and distant metastases, but an increased propensity to develop new pulmonary lesions. After resection, the long-term outcomes are very good, better than that of NSCLC with separate solid tumor nodules or solid 2nd primary NSCLCs.[15-17] The fairly common incidence of patients with multiple GG/L tumors and the multiplicity of such nodules stand in contrast to the infrequent incidence of patients with solid 2nd primary lung cancers (rarely >2), suggesting these are different entities. Finally, multifocal GG/L adenocarcinomas are relatively easily recognized both clinically and by histology. These factors led the multiple nodules subcommittee of the IASLC SPFC to specifically recognize this entity. The proposed criteria should help promote consistent reporting and future research to better understand the nature of these tumors.

Several characteristics of multifocal GG/L lung adenocarcinomas suggest that TNM classification is best using a method that has long been in existence in the AJCC/UICC manuals for multiple tumors in one organ, in which the highest T lesion defines the T category with the multiplicity of the tumors represented in parentheses – e.g. T1a(4) or T1a(m) – and a single N and M is assigned for all tumors together. These multifocal GG/L lung cancers are adenocarcinomas with a low incidence of nodal and distant metastases. They are often many lesions, making separate TNM staging of each one unwieldy.

Clinical utility is of major importance, meaning the ability to use this in daily practice for both clinical and pathologic staging. The T(#/m) classification is applicable prior to resection but also after resection by accounting for additional sub-solid nodules without necessitating resection and pathologic characterization of all lesions. This is particularly important for these patients, as it is not uncommon to resect one lesion but continue to observe others.

A binary view of separate vs related tumors may be too rigid. The frequent multiplicity of GG/L tumors suggests the presence of a common etiologic factor or factors; the frequent observation of patients with lesions of different sizes and proportions of solid components suggests that at least some steps in the process of malignant transformation occur independently. Thus, GG/L tumors may have similarities as

well as differences. The degree of similarity vs difference may best be viewed as gradations along a continuum. This supports a classification schema that avoids necessitating a detailed comparison of each lesion and a potentially difficult-to-define boundary characterized by subtle findings.

We recognize that additional clinical information may not be automatically apparent to the pathologist. However, a fundamental rule of TNM classification is that pathologic classification is "based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathologic examination".[73, 74] When a prominent lepidic component to an adenocarcinoma is present, and especially when there are multiple such lesions, the presence of a multifocal GG/L lung adenocarcinoma should be suspected; the tumors should be categorized as such if consistent with the entirety of the information pertaining to that patient.

The relationship of diffuse pneumonic-type of adenocarcinoma to multifocal GG/L adenocarcinoma is not clear. These may be different entities or just different parts of the spectrum of the same entity. Although the pneumonic form is mostly associated with mucinous (vs. non-mucinous) histology, there is some overlap; distinguishing GG/L and pneumonic-type cancers solely based on histologic subtype is not ideal. We suggest that patients with diffuse vs. multifocal nodular forms of adenocarcinoma be reported separately in order to clarify the relationship.

The diffuse pneumonic-type of adenocarcinoma is traditionally thought of as a single cancer with diffuse involvement. Therefore classification of this pattern of disease as a single T (or M1a if bilateral) is in keeping with this tradition. The decreased propensity for nodal or distant metastases supports using a single N and M for these tumors.

Many questions are unanswerable regarding multifocal GG/L lung adenocarcinoma. Are these tumors really a different type of lung cancer, or simply appear different because they are observed in a different phase of development? In other words, do GG/L cancers eventually become "typical" solid, spiculated adenocarcinomas? Are they really inherently more indolent, or does the rate of growth and propensity for metastasis change over time? The fact that patients with sub-solid nodules typically have many nodules, whereas patients with separate solid tumor nodules usually only have 1 or 2 (and no additional GGNs) suggests these are different entities. Similarly, diffuse (pneumonic or miliary) disease without the development of nodal or distant metastases appears to be a different entity than the typical solid spiculated lung cancer with frequent nodal and distant metastases. But the true nature of these forms of lung cancer and their relationship to one another is unclear.

It is important to emphasize that the TNM classification is intended primarily to provide a nomenclature for the anatomic extent of disease. How a patient should be managed is a different matter than how the tumor should be classified. Furthermore, the anatomic extent of disease is only one factor affecting prognosis; other factors include the type of cancer, the treatment given and the effectiveness thereof, patient related factors and structural (e.g. healthcare system) factors. TNM classification is only a tool to facilitate discussion of treatment strategy and prognosis.

Being able to consistently define a cohort of patients is a prerequisite to conducting and reporting investigations. Patients with multiple malignant pulmonary lesions have presented a particular challenge because of lack of distinction between disease entities with markedly different biologic behavior as well as confusion about how to apply TNM classification rules. We hope that the definitions proposed here pave the way for research that will answer the many open questions. We expect that further research will highlight aspects of the proposed definitions that need improvement. However, we believe that the currently available evidence justifies recognition of distinct patterns of disease. We believe the proposed criteria and clarification of how to apply TNM classification to these tumors represent a step forward along the path towards both scientific progress and patient management.

Conclusion

An increasing proportion of patients present with multiple tumors that have a prominent ground glass component by imaging or lepidic component by microscopy. This creates difficulties in the assignment of TNM categories. It is proposed that the T category of such GG/L tumors be classified using the T category of the highest T lesion and in parentheses either the number of GG/L tumors or simply "m" for multiple. This classification scheme should be used regardless of nuances of similarities vs differences among the GG/L tumors, recognizing that by definition these will be similar. A single N and M category is assigned for all GG/L tumors combined (the incidence of nodal or extrathoracic involvement is unusual). Both clinical information (imaging presence of additional lesions) as well as the pathologic information (from resected lesions) should be used to determine the TNM classification. Lesions that are pure ground glass and <5mm or AAH are not counted. The pneumonic-type of adenocarcinoma should be classified according to the size of the area of lung involved, or as T4 or M1a in the case of involvement of more than one lobe (i.e. either ipsilateral or contralateral). A single N and M category is assigned. Consistency in nomenclature to describe these tumors will greatly facilitate the ability to develop a greater understanding of the nature of these entities, their behavior, and how such patients should be managed.

APPENDIX

IASLC Staging and Prognostic Factors Committee

Peter Goldstraw, Past Chair, Royal Brompton Hospital and Imperial College, London, United Kingdom; Ramón Rami-Porta, Chair, Hospital Universitari Mutua Terrassa, Terrassa, Spain; Hisao Asamura, Chair Elect, Keio University, Tokyo, Japan; David Ball, Peter MacCallum Cancer Centre, Melbourne, Australia; David G. Beer, University of Michigan, Ann Arbor, MI, United States of America (USA); Ricardo Beyruti, University of Sao Paulo, Brazil; Vanessa Bolejack, Cancer Research And Biostatistics, Seattle, WA, USA; Kari Chansky, Cancer Research And Biostatistics, Seattle, WA, USA; John Crowley, Cancer Research And Biostatistics, Seattle, WA, USA; Frank Detterbeck, Yale University, New Haven, CT, USA; Wilfried Ernst Erich Eberhardt, West German Cancer Centre, University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Françoise Galateau-Sallé, Centre Hospitalier Universitaire, Caen, France; Dorothy Giroux, Cancer Research And Biostatistics, Seattle, WA, USA; Fergus Gleeson, Churchill Hospital, Oxford, United Kingdom; Patti Groome, Queen's Cancer Research Institute, Kingston, Ontario, Canada; James Huang, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Catherine Kennedy, University of Sydney, Sydney, Australia; Jhingook Kim, Samsung Medical Center, Seoul, Korea; Young Tae Kim, Seoul National University, Seoul, South Korea; Laura Kingsbury, Cancer Research And Biostatistics, Seattle, WA, USA; Haruhiko Kondo, Kyorin University Hospital, Tokyo, Japan; Mark Krasnik, Gentofte Hospital, Copenhagen, Denmark; Kaoru Kubota, Nippon Medical School Hospital, Tokyo, Japan; Antoon Lerut, University Hospitals, Leuven, Belgium; Gustavo Lyons, British Hospital, Buenos Aires, Argentina; Mirella Marino, Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, MD Anderson Cancer Center, Houston, TX, USA; Jan van Meerbeeck, Antwerp University Hospital, Edegem (Antwerp), Belgium; Alan Mitchell, Cancer Research And Biostatistics, Seattle, WA, USA; Takashi Nakano, Hyogo College of Medicine, Hyogo, Japan; Andrew G. Nicholson, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, United Kingdom; Anna Nowak, University of Western Australia, Perth, Australia; Michael Peake, Glenfield Hospital, Leicester, United Kingdom; Thomas Rice, Cleveland Clinic, Cleveland, OH, USA; Kenneth Rosenzweig, Mount Sinai Hospital, New York, NY, USA; Enrico Ruffini, University of Torino, Torino, Italy; Valerie Rusch, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Nagahiro Saijo, National Cancer Center Hospital East, Chiba, Japan; Paul Van Schil, Antwerp University Hospital, Edegem (Antwerp), Belgium; Jean-Paul Sculier, Institut Jules Bordet, Brussels, Belgium; Lynn Shemanski, Cancer Research And Biostatistics, Seattle, WA, USA; Kelly Stratton, Cancer Research And Biostatistics, Seattle, WA, USA; Kenji Suzuki, Juntendo University, Tokyo, Japan; Yuji Tachimori, National Cancer Center, Tokyo, Japan; Charles F. Thomas Jr, Mayo Clinic, Rochester, MN, USA; William Travis, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Ming S. Tsao, The Princess Margaret Cancer Centre, Toronto, Ontario, Canada; Andrew Turrisi, Sinai Grace Hospital, Detroit, MI, USA; Johan Vansteenkiste, University Hospitals, Leuven, Belgium; Hirokazu Watanabe, National Cancer Center Hospital, Tokyo, Japan; Yi-Long Wu, Guangdong Provincial Peoples Hospital, Guangzhou, People's Republic of China.

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Tables

Table 1. Glossary of Terms

Term	Definition
Ground Glass Nodule (GGN)	Focal nodular area of increased lung attenuation on a CT scan, through which normal parenchymal structures (i.e. airways and vessels) can be visualized. These are pure ground glass, with no solid component
Part-solid nodule	A discrete lung parenchymal nodule with both a ground glass and a solid component
Sub-solid nodule	A discrete lung parenchymal nodule that can be either pure ground glass or part-solid
Multifocal Ground Glass/Lepidic (GG/L) lung adenocarcinoma	Multiple discrete nodules of lung cancer that have ground glass features (either pure or part-solid) on imaging or lepidic features on histology (with or without an invasive component)
Atypical Adenomatous Hyperplasia (AAH)	Small (usually ≤5mm) localized proliferation of mildly to moderately atypical cells lining the alveolar walls
Adenocarcinoma-in-situ (AIS)	Small (≤3cm) adenocarcinoma with growth restricted to neoplastic cells along pre-existing alveolar structures and lacking stromal, vascular or pleural invasion
Minimally Invasive Adenocarcinoma (MIA)	Small (≤3cm) adenocarcinoma with a predominantly lepidic pattern and ≤5mm invasion in greatest dimension
Lepidic Predominant Adenocarcinoma (LPA)	Bland pneumocystic cells growing along alveolar walls, with an invasive component of >5mm
Pneumonic-type of lung adenocarcinoma	Pneumonia-like area of infiltrate/consolidation involving a region of the lung. Histologically this is usually predominant lepidic growth, with partial filling of alveolar air spaces by mucin or tumor cells.

Table 2: Multifocal GG/L Lung Adenocarcinoma

First Author	N	% pN2	% Re-sected	Loca-tion	% Multi focal	CT appearance (% ground glass)			% BAC[a] Histology		% 5-year Survival	
						<50%	>50%	Pure	Mixed	Pure	all	pN0
Ishikawa[25]	93	8	100	various	87	26	51	22	-	-	87	93
Vazquez[b 30]	49	10[c]	100	various	100	42	23	34	74	12	-	100
Nakata[29]	31	6	100	various	84	28	43	29	69[d]	31	93	-
Ebright[12]	29[e]	3[c]	100	various	100	-	-	-	66	34	68	-
Mun[b 28]	27	0	100	various	93	0	-	-	14	86	100[f]	100[f]
Kim[58]	23	0	100	-	100	0	0	100	0	69	100	100
Roberts[90]	14	0	100	various	100	-	-	-	14	57	64	64
Average											**85**	**91**
Registry Data												
Zell 2006[27]	93	11	91	Same L	100	-	-	-	-	-	48[f]	-
Zell 2006[27]	80	22[g]	68	Ipsi DL	100	-	-	-	-	-	25[f]	-
Zell 2006[27]	198	22[g]	21	Bilat L	100	-	-	-	-	-	7[f]	-

Inclusion criteria: studies involving multifocal lung adenocarcinoma and ≥10 patients from December 1995-April 2015.

BAC = bronchioloalveolar carcinoma; Bilat L = bilateral lobes; Ipsi DL = ipsilateral different lobe; L = lobe

[a]although the term bronchioloalveolar carcinoma has been abandoned, it was in use at the time these papers were written

[b]involving primarily patients detected by CT screening for lung cancer

[c]N1 and N2 combined

[d]Includes adenocarcinoma.

[e]patients with pneumonic (infiltrative) adenocarcinoma excluded

[f]4 year overall survival

[g]both ipsilateral and bilateral different lobes reported together

Table 3: Recurrence Pattern of Multifocal GG/L Lung Adenocarcinoma

1st Author	N	Type	Recurrence Type (%)				
			New 1º	Lung	N2,3	L+D	D
Ebright[u 12]	47	Pure GG	43	38		10	10
Mun[b 28]	27	Pure GG	100	0		0	0
Ebright[u 12]	21	>50% GG	50	30		10	10
Ebright[u 12]	32	<50% GG	62	23		0	15
Ishikawa[25]	93	Multifocal	-[c]	(53)[c]	(29)[c]	-	(18)[c]
Regnard[a 49]	61	BAC[d]	-[c]	(55)[c]	(15)[c]	-	(30)[c]
Average[e]			**64**	**23**		**5**	**6**

Inclusion criteria: studies reporting recurrence patterns in multifocal lung adenocarcinoma and ≥10 patients from December 1995-April 2015.

D = distant; GG = ground glass; L = local (intrathoracic); N = total number of patients

[u]included patients with unifocal disease

[b]involving primarily patients detected by CT screening for lung cancer

[c]data for new primary cancers not reported

[d]pre-1999 definition

[e]excluding values in parentheses

Table 4: Criteria Identifying Multifocal Ground Glass/Lepidic Lung Adenocarcinoma

Clinical Criteria

Tumors should be considered multifocal GG/L lung adenocarcinoma if:

There are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected (or proven) to be cancer.

- This applies whether or not the nodules have been biopsied
- This applies if the other nodules(s) are found on biopsy to be AIS, MIA or LPA
- This applies if a nodule has become >50% solid but is judged to have arisen from a GGN, provided there are other sub-solid nodules
- GGN lesions <5mm or lesions suspected to be AAH are not counted

Pathologic Criteria

Tumors should be considered multifocal GG/L lung adenocarcinoma if:

There are multiple foci of LPA, MIA, AIS

- This applies whether a detailed histologic assessment (i.e. proportion of subtypes, etc.) shows a matching or different appearance
- This applies if one lesion(s) is LPA, MIA or AIS and there are other sub-solid nodules that have not been biopsied
- This applies whether the nodule(s) are identified preoperatively or only on pathologic examination
- Foci of AAH are not counted

AAH = atypical adenomatous hyperplasia; AIS = adenocarcinoma in situ; GGN = ground glass nodule; LPA = lepidic predominant adenocarcinoma; MIA = minimally invasive adenocarcinoma

(Note that a radiographically solid appearance and the specific histologic subtype of solid of adenocarcinoma denote different things.)

Table 5: Pneumonic-Type of Adenocarcinoma

First Author	N	Presentation				Histology (%)			% 5-year Overall Survival			Recurrence Type (%)		
		% Bi-lateral	% N2,3	% M1b	% Re-sected	Mu-cinous	Mixed	Non-mucin	All	Resected	pN0	L	L+D	D
Wislez[76]	52	58	22	6	38	26	21	53	13	36	-	93	-	7
Okubo[69]	25	40	-	-	56	44	12	44	-	40	-	-	-	-
Regnard[49]	21	-	-	-	-	57	14	29	-	27	-	80	-	20
Dumont[81]	12	-	33	0	100	50	-	50	-	25	-	-	-	-
Ebright[12]	7	-	0	0	100	100	0	0	-	27	27	80	0	20
Casali[48]	7	-	-	0	100	86	0	14	-	28	-	-	-	-
Average										**31**		**84**	**-**	**16**

Inclusion criteria: studies reporting specifically on pneumonic-type adenocarcinoma in ≥5 patients from December 1995-April 2015.
D = distant; L = local (intrathoracic); N = total number of patients

Table 6: Criteria Identifying the Pneumonic-Type of Adenocarcinoma

Clinical Criteria

Tumors should be considered pneumonic-type of adenocarcinoma if:

The cancer manifests in a regional distribution, similar to a pneumonic infiltrate or consolidation.

- This applies whether there is one confluent area or multiple regions of disease. The region(s) may be confined to one lobe, in multiple lobes or bilateral, but should involve a regional pattern of distribution.
- The appearance of involved areas may be ground glass, solid consolidation or a combination thereof.
- This can be applied when there is compelling suspicion of malignancy whether or not the area(s) have been biopsied.
- This should not be applied to discrete nodules (i.e. GG/L nodules)
- This should not be applied to tumors causing bronchial obstruction with resultant obstructive pneumonia or atelectasis

Pathologic Criteria

Tumors should be considered pneumonic-type of adenocarcinoma if:

There is diffuse distribution of adenocarcinoma throughout a region(s) of the lung, as opposed to a single well demarcated mass or multiple discrete well demarcated nodules.

- This typically involves an invasive mucinous adenocarcinoma, although a mixed mucinous and non-mucinous pattern may occur.
- The tumor may show a heterogeneous mixture of acinar, papillary and micropapillary growth patterns, although it is usually lepidic predominant.

GG/L, ground glass/lepidic

(Note that a radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things.)

The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic-Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification

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